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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,558	03/22/2001	Lawrence H. Lazarus	209897	4487

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6780

EXAMINER

LUKTON, DAVID

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 07/21/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/814,558

Applicant(s)

LAZARUS ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,10,11 and 15-24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,10 and 15-24 is/are allowed.
- 6) ☒ Claim(s) 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 16
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Pursuant to the directives of paper No. 14 (filed 5/12/03), claims 1, 11, 19 have been amended, claims 2-9, 12-14 cancelled, and claims 21-24 added. Claims 1, 10, 11, 15-24 are pending.

Applicants arguments filed 5/12/03 have been considered and found persuasive. The previously imposed rejections are withdrawn.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the specification, data is provided which shows that the claimed compounds can antagonize the *delta*-opioid receptor *in vitro*. Claim 11 recites the term "treating" in the claimed method of use. The term "treating", in reference to a subject afflicted with a given disorder, is taken as an assertion that therapeutic efficacy can be achieved. As asserted in the specification (page 19, lines 7-8), the claimed compounds can be used to induce a state

of analgesia in a mammal. Also asserted (page 23, line 9+) is that the claimed compounds can be used to enhance the efficacy of verapamil, or asimadoline, and of chemotherapeutic agents. Thus, claim 11 would encompass a method of inducing analgesia in a mammal that is suffering from pain, and would encompass a method of enhancing the efficacy of a chemotherapeutic agent that has been administered to a mammal that is afflicted with cancer. However, there is no evidence that either of these can be achieved.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As for the "state of the art", there are examples of compounds which are effective to antagonize the *delta*-opioid receptor *in vitro*, and which also induce analgesia. However, it is not necessarily that case that if a compound can antagonize the *delta*-opioid receptor *in vitro*, that it will be effective to induce analgesia. First, the degree of antagonism may not be sufficient to achieve a perceptible effect, and second, the claimed compounds may be sufficiently vulnerable to metabolic enzymes that they will not survive long enough to reach the requisite receptor quickly enough to induce an analgesic effect. As for enhancing the efficacy of a chemotherapeutic

agent, there is no evidence that the skilled pharmacologist would have recognized, at the time of the invention, that *delta*-opioid receptor antagonists will be effective in this regard.

With respect to the matter of "unpredictability", the skilled pharmacologist would conclude that where receptor binding, receptor antagonism, and receptor activation are concerned, one cannot "predict" physiological or therapeutic efficacy on the basis of *in vitro* activity.

Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, but discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.
- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH₂ (Et): effects on opioid receptor binding and activation" (*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.
- Keith, "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.
- Xiao (*Biochemistry* **40**, 2860, 2001) has looked at the relationship between cAMP production in cells, and *in vivo* activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of *in vivo* activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased *in vivo* insulintropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase

in *in vivo* insulinotropic activity. Thus, receptor activation is not necessarily predictive of *in vivo* activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) 2 (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [125I]-Nle4DPhe7-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

Thus, it is evident that whether one has demonstrated that a given compound is effective to stimulate a receptor, or to antagonize a receptor, attempts to achieve a given physiological response using that compound lead to "unpredictable" results. In addition, there is no direction or guidance presented as to how one would use the claimed compounds to induce analgesia or to enhance the efficacy of verapamil, asimadoline, or chemotherapeutic agents. Further, there are no "working examples" which demonstrate how to use the claimed compounds to induce analgesia or to enhance the efficacy of verapamil, asimadoline, or chemotherapeutic agents. These facts, taken together with the nature of the invention, the state of the prior art, and the relative skill of those in that art, the skilled pharmacologist would conclude that "undue experimentation" would be required to practice the claimed invention.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

D. Lukton 7/16/03

Christopher S. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600